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The purpose of this proposal is to provide insight into gene environment interactions. It leverages the simplified genetics and detailed records of the military working dog population. There are several critical aspects to meeting the aims of this proposal. 1) development of data driven selection criteria, 2) biological sampling of representative dogs, and 3) generation of mathematical methodologies capable of handling heterogenous data and statistical tests in consistent manner and providing clear and understandable results that are biologically valid. Here we provide a breakdown of the previous year's work and document our progress towards achieving the specific aims we proposed. While the overall progress of this project is summarized in the Annual Report by Dr. Carlos Alveraz (Lead PI from NCHRI), here are the tasks in which I (Huang from OSU) have engaged in

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Introduction

The purpose of this proposal is to provide insight into gene environment interactions. It leverages the simplified genetics and detailed records of the military working dog population. There are several critical aspects to meeting the aims of this proposal. 1) development of data driven selection criteria, 2) biological sampling of representative dogs, and 3) generation of mathematical methodologies capable of handling heterogenous data and statistical tests in consistent manner and providing clear and understandable results that are biologically valid. Here we provide a breakdown of the previous year's work and document our progress towards achieving the specific aims we proposed. While the overall progress of this project is summarized in the Annual Report by Dr. Carlos Alveraz (Lead PI from NCHRI), here are the tasks in which I (Huang from OSU) have engaged in.

Body

Task 1- Regulatory Approval:

All institutional agreements (CRADAs) and regulatory approvals (IACUC animal protocols) are fully executed. The last of these, the final ACURO approval of the approved IACUC protocol for drawing blood samples of the Military Working Dogs (MWDs) (at the Daniel E. Holland MWD Hospital, Lackland AFB, San Antonio) was received in this reporting period.

Task 2- Data Capture of Veterinary Records: Our project Veterinary Technician working at the Daniel E. Holland MWD Hospital continued to acquire clinical and associated data from MWDs. The data are being used for i) development of data capture methods (discussed in Task 6), and ii) selection of dogs for inclusion in the study (discussed in Task 4). Even as technological/computational solutions were being developed, there was extensive collection of full health care records and scannable associated data. Because the MWD population is not static, with new dogs entering and other dogs returning, this high value task will continue until near the end of the study. This is advantageous not only to select the highest information dogs for the initial gene-environment study, but also to conduct validation studies. For example, cancer affected or unaffected littermates or step-siblings could appear at the Holland MWD Hospital, Lackland AFB, at any time.

MWD health record selection has been optimized by using birth, pedigree and pathology data. Capture and archiving of those health records is advanced for the dogs of highest interest (dogs with cancer and related dogs, and dogs of older age, but without cancer).

MWD health records were and continue to be scanned at the Holland MWD Hospital. Those records are efficiently and securely transferred to the database server at Nationwide Children's Hospital.

Task 4 Identification, recruitment, and retention of cancer bearing and control dogs.

This task is well advanced, especially in the sense of acquisition of health care records from dogs prioritized by being cancer positive, high-cancer risk by family occurrence or of advanced age. The records for our primary study subjects was essentially completed this reporting period. In addition, we have expanded our data acquisition and analysis to the full MWD population of Belgian Malinois.

Task 6- Adaptation of existing resources, data storage and hosting:

In the previous annual report, we described the development of the virtual database server for this project. That included both the functional concepts behind the database design and its high level of security. The refinement and addition of functionality continued in this reporting period.

The most important aspect enhanced in this reporting period was in the area of conversion of health care records from paper records to digital searchable data. In the previous reporting period we described the technological approach and advanced software for conversion of paper records scanned to PDF and then converted to searchable data. In this reporting period, we completed the initial design of two custom forms. That is, a custom template was made to capture the data from two standardized forms and convert most or all fields to the data types found in those fields. The software then allows for split screen analysis of the PDF copy and the raw conversion data – in this way, one can visually validate or correct the data and annotate it as "manually curated". The software and these two custom forms have been implemented within our virtual database server. These can now be accessed through password-authenticated project team members at any site.

Task 7: Pathway analysis and functional characterization.

As reported in the previous two annual reports, this task is advanced. In this reporting period, we continued to conduct broad cancer data mining studies that will be relevant to our analyses (also described in the last annual report). These types of analyses are likely to dramatically enhance our canine studies, and could serve to support our findings. This is

because there is vastly more human data available, especially in the area of somatic genetics and biochemical pathway/systems analysis.

Task 8- Project management, Quality control and assurance, and Security:

This task continues smoothly and without significant change as reported in the previous annual reports.

Key Research Accomplishments

- The final ACURO approval of the approved IACUC protocol for drawing blood samples of the Military Working Dogs (MWDs) (at the Daniel E. Holland MWD Hospital, Lackland AFB, San Antonio) was received.
- The project veterinary technician located at the Daniel E. Holland MWD Hospital was set up with all necessary equipment/supplies to collect blood samples under IACUC protocol compliance.
- MWD blood drawing by our veterinary technician at the Daniel E. Holland MWD Hospital was initiated, with successful shipping to the PI's lab at Nationwide Children's Hospital, Columbus, OH.
- Acquisition of MWD health care records from the primary study subjects in the breeding program and ongoing expansion to the consideration of the full population (i.e., of those meeting inclusion criteria).
- Used pathology records to quickly identify MWDs with cancer, and used pedigree data to identify lines suspected of increased cancer risk.
- Successful first implementation of custom forms for conversion of scanned health records to searchable digital data (optimization ongoing).
- Successful implementation of health records digital-conversion software in our virtual database server, and password-authenticated access from all local and remote team members.

Reportable Outcomes

- Former project team member Dr. Jennie Rowell, having received her PhD from OSU for her work at NCHRI (PI Alvarez's dissertation research advisee) and completing her postdoctoral fellowship at NIH, began her tenure track Assistant Professor position at the College of Nursing, OSU (see Appendices).
- The software engineer Jacob Aaronson left OSU at the end of August 2014. A new software engineer will be appointed once the no-cost extension application is approved.

Conclusion

The project is now advanced in all fronts. The most important development was the initiation of blood drawing of MWDs. Another important development was the implementation of a software package for conversion of scanned health records to searchable digital data.

Acquisition of health records is essentially complete for the primary study subjects, and we have expanded the study to consider all dogs of the MWD population that meet inclusion criteria.

We have enhanced other necessary genetic analysis methods to the point where almost all methods we will use for the major final analyses have been implemented successfully with very highly relevant canine cancer and canine breed data. That now includes analyses of single breed population structure and of gene-gene interactions.